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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GUCKER, STEPHEN	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,844	HAGEN ET AL.	
	Examiner	Art Unit	
	Stephen Gucker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *18,22-28,31,32 and 47-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,19-21,29,30 and 33-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/25/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group I, claims 1-17, 19-21, and 29-46 in so far as they are drawn to a method for identifying an agent that alters processing of APP by contacting an agent with a cell in the reply filed on 11/7/07 is acknowledged. Further, Applicant elects with traverse APPs-β as the species of APP; β-secretase as the APP processing enzyme, and CD24 as the presentation molecule (which is claim 30, but not claim 31 (IL-3 receptor) or claim 32 (thioredoxin) as presentation molecules). Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 18, 22-28, 31-32, 47-60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention (species for claims 30-31), there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/7/07.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1-2, 8-15, 42-43, and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Mucke et al. (US 6,175,057 B1; IDS reference AD (filed 9/25/07); "Mucke"). Mucke discloses methods using transgenic animals or cells derived therefrom to identify candidate agents that modulate phenomena associated with Alzheimer's disease (AD) such as amyloid deposition (which results inherently from the processing of amyloid precursor protein (APP)) (column 13, line 62 to column 15, line 20; and column 16, line 1 to column 17, line 17). These candidate agents are disclosed as being from compound libraries, combinatorial libraries, natural product libraries, small molecules, biomolecules, and peptides (instant claims 8-15)(column 16, lines 19-58). Labeled antibodies may be used to quantify amyloid proteins in neurite plaques or cells (instant claims 42-43) (column 16, line 59 to column 17, line 17). Allosteric effectors of APP would be identified by the prior art methods as inherently as other inhibitors would be identified by the prior art methods (the process steps of the screening assay are capable of identifying a broad genus of inhibitors).

5. Claims 1-7, 36-39, and 45-46 are rejected under 35 U.S.C. 102(e) as being anticipated by Gurney et al. (US 6,440,698 B1; IDS reference AH (filed 9/25/07); "Gurney"). Gurney discloses methods for identifying inhibitors of an enzyme that cleaves the β-secretase cleavable site (instant claims 3-4) of amyloid precursor protein (APP) from an animal host cell that expresses APP and β-secretase and measuring the release of amyloid beta-peptide (Aβ) into the culture medium and accumulation of C-terminal fragments (CTF99) in cell lysates (instant claim 2)(column 10, lines 31-59). Aβ1-42 peptide is a form of Aβ peptide disclosed as being particularly amyloidogenic

and thus very important in Alzheimer's Disease (AD) (instant claims 5-7) (column 1, line 42 to column 2, line 24). Gurney also teaches recombinant animal isolated host cells (instant claims 36-38) used in the instant methods (column 7, lines 28-46 and column 36, lines 14-21), and the use of a flow sorter (instant claim 46) (column 35, line 7 to column 36, line 45) and carrying out the method with living cells in a culture medium (instant claim 39) (column 10, lines 30-59). Allosteric effectors of APP would be identified by the prior art methods as inherently as other inhibitors would be identified by the prior art methods (the process steps of the screening assay are capable of identifying a broad genus of inhibitors).

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1, 13-17, 19-21, 29, and 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gurney in view of Nolan (US 2002/0127564, IDS reference AI (filed 9/25/07); "Nolan"). The teachings of Gurney are as set forth in **¶5** above. Gurney does not teach a method of identifying peptide agents/inhibitors wherein the peptide is encoded by oligonucleotides of about 18 to about 120 nucleotides or of about 36 to about 60 nucleotides. Nolan teaches methods for identifying bioactive agents from translation products (instant claims 13-15) ranging from about 4 amino acids in length (equivalent to about 12 nucleotides) to about 100 amino acids in length (equivalent to about 300 nucleotides). Especially preferred embodiments are about 18 to about 60 nucleotides in length (instant claims 16-17) (page 2, paragraphs [0025-0026]). Said nucleotide sequences of Nolan can be from expression libraries comprising randomized expression products, and include a fusion presentation partner (instant claims 19-20 and 29) (page 2, paragraphs [0026-0028]). Furthermore, this fusion protein can comprise marker epitopes such as polyhistidine and myc (instant claims 33-34) (page 5, paragraph [0035]) or a membrane anchoring glycophosphatidylinositol (GPI) (instant claim 35) (page 4, paragraph [0045]). It would have been obvious at the time the invention was made for one of ordinary skill in the art to use the methods of Gurney for screening of inhibitors of an enzyme that cleaves the β-secretase cleavable site of APP from an animal host cell that expresses APP and by using the encoded peptides with sequence length as suggested by Nolan because Nolan discloses that small peptides (that is, peptides encoded by about 18 to about 60 nucleotides in length) can be conformationally constrained into "presentation structures" which "will benefit both the

later generation of pharmaceuticals and will also likely lead to higher affinity interactions with the peptide with the target protein" ([page 2, paragraph [0029]); the target protein, being in the instant case, β-secretase. Furthermore, it would also be obvious to try to use expression libraries that are pre-enriched for oligonucleotides encoding peptides that specifically bind to APP because the aim of the teachings of Gurney is to find inhibitors of APP processing in order to treat AD, and peptides that bind to APP would have the capability of interfering with the binding of β-secretase to APP and block the enzyme from cleaving the APP substrate. The advantage of small peptides that Nolan teaches renders instant claims 1, 13-17, 19-21, 29, and 33-35 *prima facie* obvious in conjunction with Gurney.

7. Claims 1, 13-15 and 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gurney in view of Nolan (US 2002/0127564, "Nolan") and further in view of Poncet et al. (IDS reference BR (filed 9/25/07); "Poncet"). The teachings of Gurney and Nolan are as set forth in **¶5** and **¶8** above, respectively. Additionally, Nolan teaches membrane anchoring sequences such as the glycosylphosphatidylinositol (GPI) anchor (page 4, paragraph [0045]), which can be used to target particular peptides to the cell membrane so that the target peptides can interact with other membrane proteins. Nolan does not teach the specific CD24 presentation molecule which has a GPI anchor. Poncet teaches the CD24 presentation molecule, including its GPI anchor, and Poncet further discloses that CD24 is expressed by human brain neurons. It would have been obvious at the time the invention was made for one of ordinary skill in the art to use the methods of Gurney and Nolan for screening of inhibitors of an enzyme that

cleaves the IDS reference AD (filed 9/25/07);-secretase cleavable site of APP from a host cell that expresses APP and β-secretase by using the CD24 presentation molecule as taught by Poncet because the APP/β-secretase interaction occurs at the cell membrane and Nolan discloses that GPI anchors are useful for targeting proteins to the cell membrane and Poncet discloses that human brain neurons normally express CD24 during their development and that CD24 comprises a GPI anchor. Absent evidence to the contrary, it would have been obvious to select CD24 as a GPI anchor presentation molecule because the invention is drawn to screening therapeutic agents for AD which only occurs in humans and CD24 is a naturally occurring GPI anchor in human neurons.

8. Claims 1 and 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gurney and Nolan as applied to claims 1, 13-17, 19-21, 29, and 33-35 above, and further in view of Mazur-Kolecka et al. (IDS reference BJ (filed 9/25/07); "Mazur-Kolecka"). Gurney and Nolan do not teach methods using blood serum or CSF. Mazur-Kolecka does teach methods of studying β-amyloid processing and deposition using both serum and CSF and Mazur-Kolecka discloses the differential effects of each on the assay methods. It would have been obvious at the time the invention was made for one of ordinary skill in the art to use the methods of Gurney and Nolan for screening of inhibitors of an enzyme that cleaves the β-secretase cleavable site of APP from an animal host cell that expresses APP and β-secretase by also including the use of serum or CSF in the assay system because Mazur-Kolecka discloses that the presence of serum can worsen the disease process while the presence of CSF can lessen the disease process of β-amyloid processing and deposition. Because such information

would be relevant for the clinical development of therapeutic agents, the teachings of Mazur-Kolecka render the instant claims *prima facie* obvious.

9. Claims 1-2 and 42-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gurney in view of Mucke. The teachings of Gurney and Mucke are as set forth in **¶5** and **¶4** above, respectively. Additionally, Gurney teaches methods using at least two different antibodies for at least two different epitopes of APP and generating standard curves for quantifying amyloid peptides from cell culture supernatants (column 35, line 7 to column 36, line 45). Gurney does not teach double antibody methods involving the cell surface. Mucke does teach quantifying amyloid peptides by using antibodies at the cell surface (column 16, line 59 to column 17, line 17). It would have been obvious at the time the invention was made for one of ordinary skill in the art to use the methods of Gurney for screening of inhibitors of an enzyme that cleaves the β-secretase cleavable site of APP from an animal host cell that expresses APP and β-secretase with double antibodies for different epitopes at the cell surface as taught by Mucke in order for Gurney to confirm and correlate the various amounts and ratios of different APP products (such as Aβ1-40 and Aβ1-42, see Tables 2, 3, 3B, and especially Table 4 (ratio of Aβ1-42/total Aβ)) that are produced in the assay system as a control to make sure the assay system is accurate, i.e. the amounts of soluble fragment released should correlate with the amount of APP fragments left behind in the cell membrane. Allosteric effectors of APP would be identified by the prior art methods as obviously as other inhibitors would be identified by the prior art methods (the process steps of the screening assay are capable of identifying a broad genus of inhibitors).

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Gucker whose telephone number is 571-272-0883. The examiner can normally be reached on Mondays through Fridays from 0930 to 1800.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen Gucker

April 4, 2008

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1648